# FINAL REPORT FOR MEDICAL MONITORING PROGRAM FOR THE ATOCHEM CLASS POPULATION

November 30, 2008

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## I. Original Medical Monitoring Request

The request for proposal defined the key elements to be provided in a medical monitoring program to evaluate residents and workers of the Atochem class area with respect to potential health effects of arsenic and other chemicals utilized and produced at the facility over the period 1932 to 1992. The successful bidder Scott & White Clinics was required to describe how they would provide the specified services. This description included details of administrative aspects of the services to be rendered including medical staffing, support staff, recruitment of residents and workers in the specified area, and frequency and duration of monitoring. Specific key personnel were identified with brief descriptions of their qualifications to implement the proposal. In addition, facilities and equipment that were utilized in providing the services were also described. A detailed budget including costs of personnel, space, document management, and laboratory tests was provided.

## II. Background

The Atochem facility located in Bryan, Texas has existed in one form or another and under various names since the late 1930's. A variety of compounds were utilized as starting materials in a variety of products that were produced during the operation of the facility. These include arsenic, manganese, and zinc based pesticides. In addition, various pesticides and organic solvents were also employed at the facility. The organic pesticides included carbamates such as Maneb, Ziram and Penncozeb and organo- phosphates including methyl parathion. Various organic solvents were also employed in the preparation of these compounds.

Relatively little is known about the long term health effects of many of the pesticides handled and produced at the facility. In general some of these compounds have received evaluation as potential carcinogens. In addition, potential for neurotoxicity from chronic exposure as well as developmental toxicity is also of concern.

While these organic compounds previously mentioned are suspected of causing health problems, arsenic is a class A carcinogen (established human carcinogen), it is also associated with a variety of non-malignant disorders. For this reason a more detailed description of the toxicology of arsenic follows. Arsenic has been recognized as a toxic substance for over two thousand years. Reports have linked arsenic with cancer since the late 19th century (IARC, 1980). In the early 1930's Eastman (1931) showed that arsenic appears in maternal blood and crosses the placenta to the developing fetus. Reports have also shown arsenic affects a wide variety of organ systems in the production of non-malignant disorders.

**Summary of Health Effects**

Arsenic and Cancer

Evidence for cancer based upon human epidemiologic studies has clearly established skin, lung, liver, bladder and kidney as being caused by exposure to arsenic. Risk assessments conducted by both the Occupational Safety and Health Administration and the Environmental Protection Agency, as well as the International Agency for Research on Cancer classify arsenic as a human carcinogen. Quantitative risk estimates are well established for lung and skin cancer from airborne exposure. Quantitative risk estimates are well established for exposure to arsenic in water. Quantitative risk estimation for air exposure for liver, kidney and bladder cancer is possible by extrapolation from water data.

Arsenic and Non-Malignant Disorders

There are a range of non-malignant conditions associated with exposure to arsenic, these include cardiovascular disorders, kidney, liver, and skin conditions. Most of this data, like that previously discussed under cancer has been in populations with elevated levels of exposure to arsenic either via air or water. A significant proportion of the literature on non-malignant disorders and arsenic comes from studies of populations exposed to elevated levels of arsenic in drinking water.

Long term consumption of water containing elevated levels of arsenic has been observed to cause increased risk of vascular degeneration, primarily in the extremities. Peripheral vascular disease may appear in early stages as Raynaud's phenomenon and may progress to acrocyanosis and gangrene. Studies also have reported liver disorders including hepatomegaly, abnormal serum liver enzyme levels, as well as portal hypertension and cirrhosis. Non-cancerous skin lesions are also associated with systemic ingestion of arsenic. It is not clear whether these can be considered sentinel lesions of future increased risk for skin or other cancers, although they certainly should be considered indicative of significant exposure.

Neurologic disorders are well associated with acute and chronic exposure to arsenic and may effect either the central or peripheral nervous system (CNS, PNS). CNS effects have been described including impaired cognition and changes in affect. Peripheral neuropathies that have been observed include axonal degeneration and occasionally segmental demyelination. Severe cases have been confused with Guillan- Barré syndrome.

A recent study of individuals exposed to arsenic in drinking water in Taiwan observed an excess risk of Diabetes Mellitus (14). The study found risks as high as 900% greater prevalence in the high exposure population compared to a population with low levels of arsenic. This study should also be viewed in light of collaborating studies in animals exposed to arsenic in providing a possible biologic mechanism for the observed finding (3).

Health Effects of Pesticides

In addition to arsenic, a variety of pesticides were produced and handled at the Atochem facility. In general the human epidemiologic literature on the chronic health effects of long term exposure to pesticides is limited. Studies have reported associations with several forms of cancer including leukemias and lymphomas. There has also been suggestion in a number of studies to associations with increased risks of adverse reproductive outcomes. On theoretical basis there is also reason to consider the possibility of long term neurologic effects similar to those seen with chronic solvent exposure.

Routes of Exposure

The exposure of residents of the Atochem area to arsenic and pesticides could have been through three possible routes: through the respiratory tree, through the gastrointestinal tract, and through the skin. The disposition of inhaled particles is determined by the size of the particles and by their solubility. The larger aerosol particles are deposited in the upper airways and eventually are expectorated or swallowed thereby entering the gastrointestinal tract. The smaller particles are deposited in the alveoli where they remain permanently or are transported to the tracheobronchial lymph nodes and remain in the nodes. Arsenic and other chemicals can

also directly enter the gastrointestinal tract via the ingestion of contaminated water, fruits and vegetables.

In the course of the evaluation of environmental exposure, particularly to arsenic in the community surrounding the Atochem facility, it was the opinion of the plaintiffs' experts that the primary route of exposure was through inhalation of airborne arsenic particulate. While dispersal would have been expected to occur during plant operation, with the cessation of the arsenic operations in 1992 this source no longer continues. It must however be pointed out that significant deposition of arsenic has been detected at levels in excess of 100 ppm in attic spaces of some structures near the facility. Therefore the potential for exposure still must be recognized to exist in attics and utility closets in these dwellings.

Endpoints of Interest

In summary, the following organ systems appear to be at the greatest potential risk:

1) Pulmonary System: carcinoma of the lung, pulmonary fibrosis, tracheobronchial and sinus abnormalities
2) Urinary Tract: bladder and renal tumors
3) Hematopoietic/Lymphoid System: lymphoma, aplastic anemia/preleukemia, leukemia
4) Liver: hepatic fibrosis, portal hypertension, cirrhosis
5) Cardiovascular System: increased risk of myocardial infarction, peripheral vascular disease
6) Nervous System: CNS - impaired cognition changes in affect, PNS peripheral neuropathies

7) Reproductive System: Congenital malformations, increased risk of spontaneous abortion

8) Pancreas: Increased risk of adult onset diabetes mellitus

Populations at Potential High Risk

The individuals who were likely to be at highest risk were those residing closest to the plant, especially those who lived within one mile. This estimate is based on the air models of the dispersion of arsenic in the area around the plant and is assumed to represent the pattern of air dispersal of all toxics from the facility. Other individuals at increased risk for the potential effects of arsenic exposure are cigarette smokers and individuals exposed to chemical toxins either at work or at home. It seems logical that individuals with the longest exposure time will be at greater risk than those with a short exposure time. Children raised in the area around the plant should also be included in the high risk category. Estimates of the level of relative risk can be estimated by the exposure matrix (Appendix I). The matrix is designed to score the relative peril of members of the class.

## III. **Comprehensive Medical Examination**

Introduction

Since persons living near or working near the Atochem facility in Bryan, Texas may have been exposed to arsenic dust and other pesticides they may be at increased risk for diseases related to these exposures, a comprehensive medical examination will be conducted for all willing individuals living or working within the 5 nanogram plume boundary. The purposes of this initial medical evaluation will be:

1) To provide a comprehensive assessment of the current state of health of these individuals.
2) To provide a comprehensive assessment of the estimated risks for developing disease among these individuals.
3) To inform individuals living or working near the Atochem facility about their modifiable risk factors for disease and to motivate them to seek follow-up care.
4) To evaluate the need and determine the frequency and scope of further medical monitoring.

**Recruitment of Subject Participation in This Program**

Clearly the most important aspect of this project and in some ways the most difficult was to obtain the participation of as many individuals who resided and/or worked in the class certification area in the medical screening and follow-up program. This problem was approached from a variety of complimentary aspects and involved the coordination of recruitment efforts with the office of the Special Master.

All identified potential participants, were contacted by letter, sent to the home of eligible individuals describing the project as well as how participation can be effected. These letters provided information on potential health risks and on the monitoring program.

<u>Word of Mouth Referrals</u>

After patients were screened or attended one of the meetings described above, individuals were encouraged to promote the project among their friends and neighbors. Word of mouth references can be a very effective means of encouraging participation in this project.

Communications Through the Media and Other Public Means

The monitoring program and the reasons for it were described to all local news media and to media in Bryan/College Station and Brazos County.

Number of Residents/Workers Eligible for the Program

Information as of 1994 indicated that approximately 26,000 individuals resided in the class certification area. It is estimated that in excess of 7,000 individuals are employed in the class certification area. It is reasonable to expect there may be significant overlap of these two eligible groups. Actual participation, based upon experience with similar situations in different parts of the country suggest 5 to 10% of those eligible might be expected to participate in the medical monitoring, although this could either be a significant over or underestimation.

**Initial Examination for Adults**

A comprehensive history and physical examination will be performed on all eligible and interested adults by the nursing staff and a qualified board-eligible or board-certified internist or family practitioner. The examination will be conducted in two parts, each part performed at separate visits about one week apart. An explanation of the examination, laboratory, and reporting procedures must be provided to all participants prior to the examination by the

provider. Examinees will then be asked to read and sign a consent statement detailing these procedures and policies. Examinees had blood and urine samples obtained for laboratory tests. Information was obtained on to reflect to following background information:

- Complete demographic data
- Educational attainment
- Residence history from 1932 through the present (This information will be collected using questions and format provided by the Trustees - for eligibility purposes)
- Current habits (smoking, other tobacco use, alcohol intake, drug use)
- Habitual household and recreational activities
- Family medical history (parents, grandparents, aunts, uncles, brothers, sisters, children)
- Estimated illness and disability days
- Occupational history

While the questionnaire may be self-administered, a project nurse reviewed the questionnaire with the examinee at the conclusion of visit one to make sure it is complete and legible.

The second part of the adult examination included a detailed history and physical examination performing by the examining physician or physician's assistant (PA). The examining physician or PA reviewed the data obtained from the questionnaire completed prior to the first visit. Then a history of current health symptoms, a past history of illnesses and operations, a history of medication use, a reproductive history, and a history of emotional problems was taken. The physician or PA performed a detailed review of systems.

Next, the physician/PA performed a comprehensive physical examination of all organ systems. The external ear canal was examined visually. A standard examination of the conjunctiva, iris, and pupils was performed. Fundoscopy was performed without dilatation. The nose and oral cavity was examined visually and manually for disease, especially leukoplakia or early cancers. The neck was examined for carotid pulses or bruits, enlarged lymph nodes, and thyroid enlargement or nodules. Standard examinations of the heart and lungs were performed. The neck, supraclavicular fossae, axillae and groins was examined for lymph node enlargement. The abdomen was examined for liver or spleen enlargement as well as for masses or aneurysm. Examination of the extremities was performed to include joint function and presence or absence of swelling or tenderness. The skin was examined for evidence of sun damage or other signs of potential or existing skin cancers. A screening neurological examination was performed consisting of an examination of each of the corneal nerves, upper and lower extremity strength examinations, and touch and vibration senses in all extremities. At the conclusion of the examination, the physician reviewed his/her examination findings with the patient and also informed the patient of the results of the laboratory.

Laboratory Test of Adults

The laboratory and other procedures to be performed for all adult subjects are detailed below. The following routine blood and urine tests will be performed:

- Complete blood counts (WBC, RBC, hemoglobin, platelets)
- Reticulocyte count

- Chemistry profile (electrolytes, BUN, creatinine, uric acid, glucose, total protein, albumin, globulin ratio, total and direct bilirubin, SGOT, SGPT, calcium, phosphorus, alkaline phosphatase, iron, total cholesterol, HDL-cholesterol, and triglycerides)
- Routine urinalysis
- Spot morning urine collection for total protein and creatinine.

All blood samples will be obtained using sterile technique according to the universal precautions published by the CDC (6,7). Examinees were informed that their blood samples would be analyzed for the tests listed above.

All men and women above the age of 40 were provided with Hemoccult II cards for detecting occult blood in the stool at the conclusion of the first visit.

**Initial Examination for Children**

There were four parts to the pediatric evaluation. The first part consisted of an explanation by the pediatric project nurse of the examination, laboratory, and reporting aspects of the program. The second part consisted of the completion of an appropriate questionnaire by the pediatric nurse together with the child and the child's parents. The third part was a detailed history by the child's own physician and a review of the history obtained by the pediatric nurse clinician. The fourth part was a physical examination with the collection of data. Children had a complete physical examination.

Laboratory Tests of Children

Because young children have a smaller blood volume than adults, the blood tests to be done will not be as extensive as in adults. No more than 5% of blood volume will be drawn at any one time.

The following laboratory tests will be done on all children:

- Complete blood counts (WBC, RBC, hemoglobin, red cell indices, platelet count).
- Reticulocyte count.
- Urinalysis.

Children 12 years and older will have the same blood and urine tests as done in adults.

**Data Management**

Participants were assigned a random number as the first step in the data collection process. All information subsequently collected for each individual will carry this number and not the patients name or identifying demographic information. The code matching name and number will be kept in a secure place.

As data was entered, they were edited and any suspicious values were rechecked against paper records for accuracy.

Since each data item is edited at entry into the computer, subsequent editing should consist of checks for completeness and checks for receipt of all records and data forms. Reports will be generated on a regular basis, e.g. monthly and quarterly, and will summarize the number of patients entered to date and provide a synopsis of the findings. Any identifying

information of examinees will be carefully deleted from the reports. Hence while the entire data set will be available for review, the privacy of individuals will be protected.

**Reporting and Follow-up for Adult Participants**

For each participant in the medical monitoring program, questionnaires, medical examinations and laboratory reports were sent by mail from Scott & White to Environomix. This information was reviewed by a physician boarded in internal medicine and occupational and environmental medicine, and a report was prepared for each participant. This complete written report was subsequently mailed to each individual, Scott & White Clinic and if designated their personal physician. We believe that examinees should receive all the information collected about them. Thus, project staff photocopied the questionnaire and physician examination form and laboratory results for attachment to their report.

**Reporting and Follow-up for Pediatric Residents**

Reports were reviewed and prepared in a similar manner to those for adults. Reports of findings were sent to the child's parents.

**Medical Monitoring Program**

The medical monitoring program was carried out on all participants who were medically evaluated as part of the Atochem Medical Monitoring Program. The results of each of the three rounds of medical examinations, was included in the final analysis. A total of 329 individuals initially signed up to participate in the Program. The first round was carried out in fall 2002 and winter 2003, the second round in fall 2004 and winter 2005 and the final round in the fall 2006

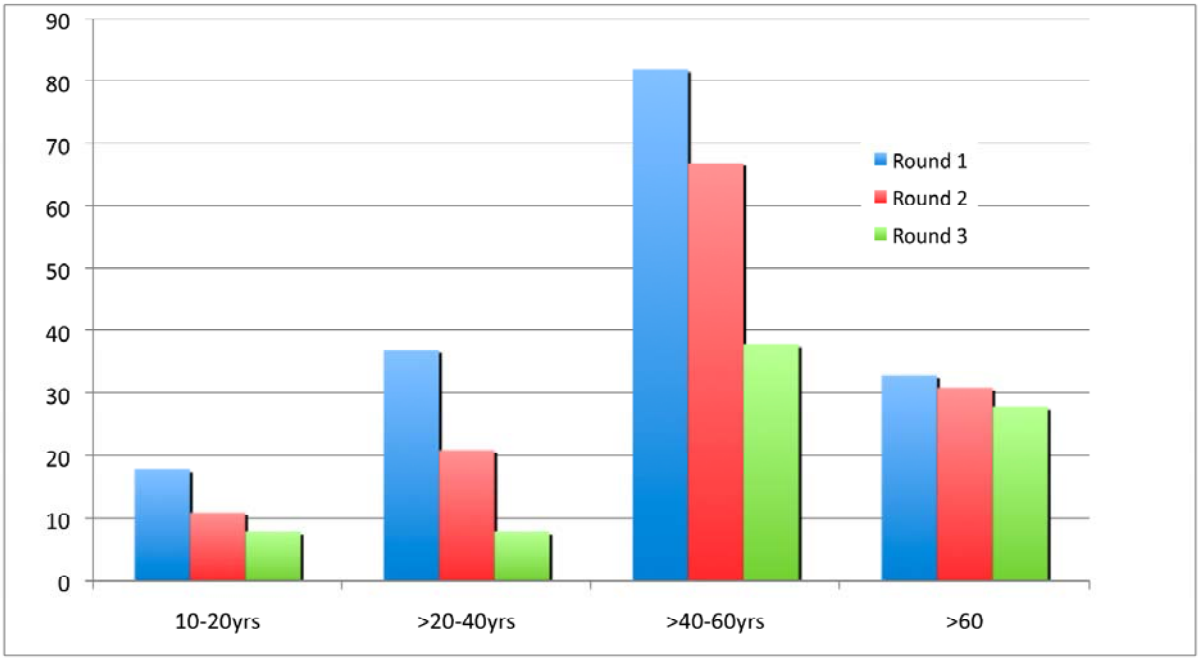
and winter 2007. Since some subjects were late to participate in some rounds, some flexibility in the timing occurred. In the first round a total of 170 participants were evaluated, 130 in round two and 82 in round three. A breakdown by gender is provided in Table 1. A total of 382 monitoring examinations were carried out on 221 individuals who actually took part in the Atochem Medical Monitoring Program representing 67% of those who initially signed up for the program. The number of participants who completed all three rounds of monitoring was 46, while 96 individuals participated in at least two rounds of the three rounds of medical monitoring.

**Table 1: Number of participants by round and total number of examinations.**

| Round | Male | Female | Total |
|---|---|---|---|
| **1** | 91 | 79 | 170 |
| **2** | 57 | 73 | 130 |
| **3** | 41 | 41 | 82 |
| **Total** | 189 | 193 | 382 |

The age range of participants in the surveillance program was from 10 to 91 years of age. The mean age of participants varied by gender and round from a low of 44 for males in round 1 to a high of just under 53 years of age for males in round 3. The age distribution, for each of the three rounds of the medical monitoring program is presented in Figure 1.

**Figure 1: Number of Participants by Age Group for Atochem Medical Monitoring Participants by Round of Monitoring Program**




The results of the medical examinations and laboratory results were evaluated for any abnormalities in the medical monitoring cohort. In particular neurologic function, skin abnormalities and liver function tests were focused on as sentinel endpoints because of their previously discussed association with arsenic toxicity. The results are summarized in the tables and figures found below.

Skin

The study participants exhibited some increased frequency of skin abnormalities, particularly in rounds 1 and 3 (See Table 2). This should not, however, be viewed as a cause for concern in that the findings virtually entirely consisted of either benign scars or from exposure to the sun which would be expected to be found in central Texas. The variability of the frequency of the reported findings in the physical examinations of participants' skin is most likely due to the

evaluation not having been always conducted by a physician, thus increasing the variability of the reporting. Of greatest importance was the absence in the study population of any excess of hyperkeratosis that would have been an indication of early stages of skin cancer associated with arsenic exposure.

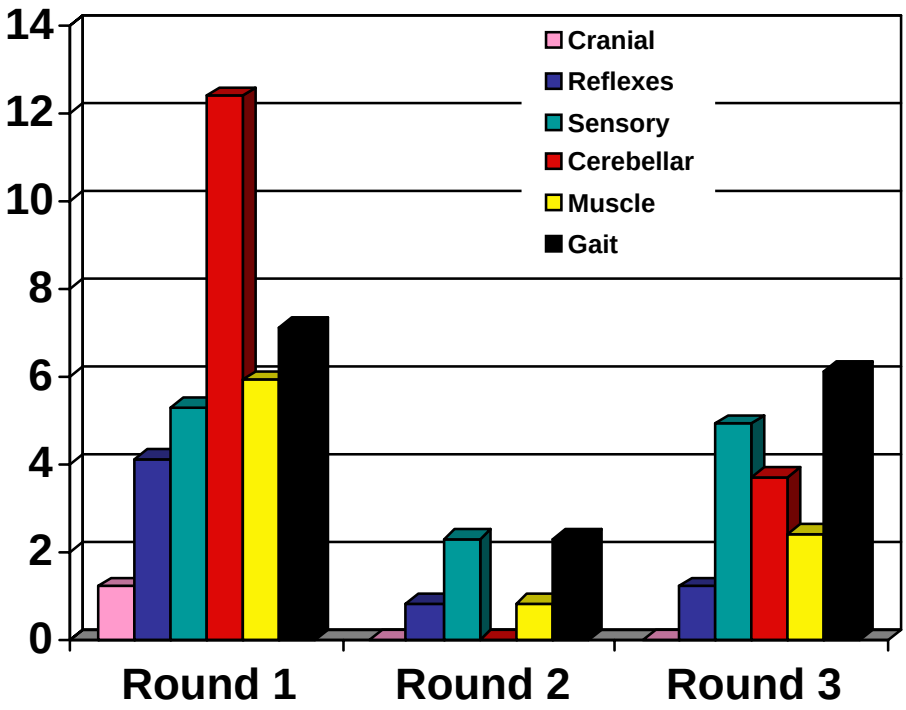
**Table 2: Number (%) of Skin Abnormalities for all rounds.**

| Normal Findings | Round 1 | Round 2 | Round 3 |
|---|---|---|---|
| **Yes** | 22 (12.3%) | 5 (3.8%) | 12 (14.6%) |
| **No** | 170 (87.7%) | 125 (96.2%) | 70 (72.3%) |

Neurologic Findings

A variety of symptoms were evaluated to determine if any pattern of abnormalities were present in the monitoring participants consistent with the effects of arsenic on the either the peripheral or central nervous system. These consisted of findings in relation to cranial, cerebellar, sensory and reflex functions, as well as possible abnormalities in muscle strength and gait (See Figure 2). In general all of these symptoms were only present in a small percentage of the participants (less than 7%) with the one exception being cerebellar findings in the first round. It is also important to keep in mind that multiple symptoms may have been found in the same individual. Overall among all the participants the vast majority of the neurologic findings were in individuals with a reported medical history of diabetes. There does not appear to be sufficient reason to interpret the frequency of the findings in this population as being associated in any way with the arsenical releases from the Atochem facility.

**Figure 2: Percent of Participants (by Round) Identified with Positive Neurologic Symptomology.**

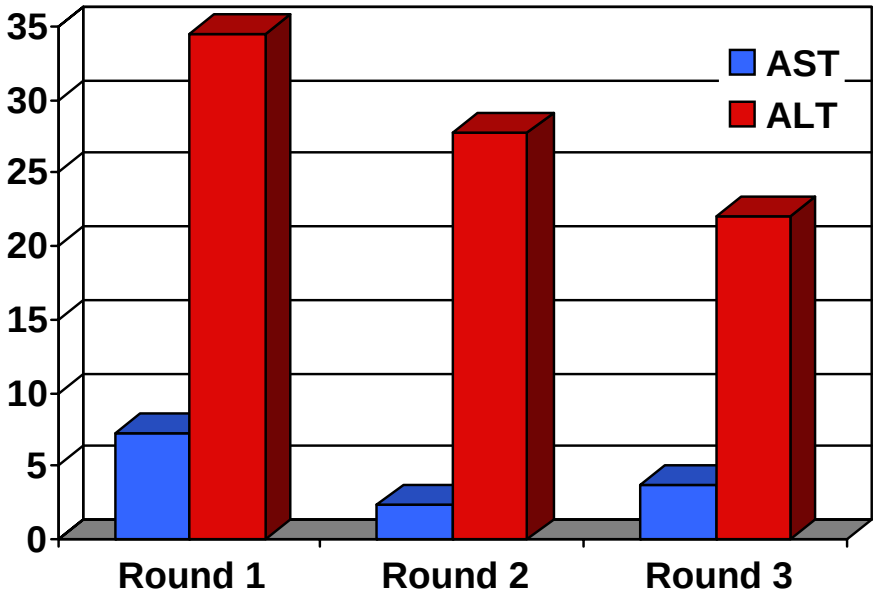



Liver Function Tests

The blood tests revealed the only consistent abnormality in the monitoring cohort. The most frequent abnormality noted was elevations in the alkaline phosphatase levels. Because this can be due to a wide range of factors, little import or attention was given to this finding. Of greater concern are the consistent increased levels of alanine aminotransferase (ALT) across all three rounds of testing. While the elevations of numerous participants were minor, the overall frequency of elevated ALT levels approached 30% (29.52% actual). In a healthy population this number would be expected to be less than 10% with elevated ALT levels. There are several

possible health factors that may contribute to these findings, among them are obesity, metabolic syndrome, nonalcoholic fatty liver disease and diabetes. However, in populations with elevated exposures to arsenic, a recognized finding that has been reported is elevated ALT levels. While these studies have been in populations whose level of arsenic exposure is far higher than any estimated exposures in the Atochem settlement area, the possibility that the observed abnormally high levels of ALT may be attributed to the arsenic released from the plant cannot be excluded. It must, however, be pointed out that those with the very mild elevations of ALT (which constitutes the primary observation in those participating in the medical monitoring program) are not of any known clinical significance.

**Figure 3: Percent of Participants (by Round) with Elevated Liver Enzyme Tests ( AST and ALT).**



Miscellaneous Findings

In general, the population that enrolled and participated in the medical monitoring program had relatively few general health problems that are not typical for a central Texas population. The occurrence of obesity and diabetes were among the more common health problems, with a few cases of Parkinson's disease, in general confined to the elderly. The only other finding of note was that depressed white blood counts were noted to occur with uncommon frequency during the second round of monitoring, but not the first or third. This was interpreted as being most likely attributable to a viral infection passing through the community/population.

Conclusions

The Atochem Medical Monitoring Program, as planned, spanned a period of 5 years. Given the number of individuals who had chosen to initially sign up for the program the percentage of individuals who actually took part is consistent, if not slightly greater than observed in other similar settlement medical monitoring programs. It is not unusual for participation to drop across the rounds, as was observed here. In some ways this is inevitable, particularly given the relative lack of findings of significant disease in the population. The overall findings should be viewed as reassuring to the Atochem settlement population that no significant health problems were uncovered over the course of the program. Even though the possibility of some health issues that have long latency periods between exposure and disease, particularly cancer, may emerge at a future date, there is currently no suggestion that this appears to be a problem at the present time. Those who lived in the Atochem settlement area should remain vigilant with regards to the

most common types of cancer associated with arsenic, skin, lung and gastrointestinal cancers and have regular physical examinations.

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